Take A Deep Breath: Lung Infection and Cognition in Down Syndrome

Michael E. Yeager
Pediatrics-Cardiology; Bioengineering
Disclosure

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- Jerome LeJeune Foundation
- Jayden DeLuca Foundation
- Celgene, Inc.
- American Heart Association
- Linda Crnic Institute for Down Syndrome
Morbidity and Mortality in Persons with Down Syndrome Manifests Predominantly as Infectious Lung Disease


<table>
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<td>Malignancies, all</td>
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<td>1.4</td>
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<td>NS</td>
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<td>Other congenital malformations</td>
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<td>1.6</td>
<td>17.1</td>
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<tr>
<td>Number of deaths</td>
<td>175</td>
<td>370</td>
<td>105</td>
<td>0.001</td>
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<td>NS</td>
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In DS, is the problem the lung, the immune system, or both?
The Lung is Overlooked in DS

Infectious lung disease accounts for 54% of hospital admissions for persons with DS

Average length of admission is 2-3 times longer than those without DS

Persons with DS have increased frequency of respiratory tract infection (62 fold higher rate)

Increased risk for acute respiratory distress syndrome
  16 fold, 8 fold, 335 fold more likely to be hospitalized, intubated, or to die, respectively

Infectious respiratory disease accounts for more deaths in DS than any other medical condition; 12 times more likely to die than typical population
Lung Health is Front and Center for Persons with DS and Their Families

Ever Made A Croup Tent At Home? I Did Every Year From 1983-2004

So What’s the Mission, the Goal?

1. Awareness! Persons with DS, autoimmunity, & lung disease
2. Learning how Trisomy 21 leads to respiratory & autoimmune diseases will help those with DS and those without DS

Folks with DS will feel better-physically & mentally
Influenza-related complications continue to be a major cause of mortality worldwide. Due to unclear mechanisms, a substantial number of influenza-related deaths result from bacterial superinfections, particularly secondary pneumococcal pneumonia. Here, we report what we believe to be a novel mechanism by which influenza-induced type I IFNs sensitize hosts to secondary bacterial infections. Influenza-infected mice deficient for type I IFN-α/β receptor signaling (Ifnar−/− mice) had improved survival and clearance of secondary Streptococcus pneumoniae infection from the lungs and blood, as compared with similarly infected wild-type animals. The less effective response in wild-type mice seemed to be attributable to impaired production of neutrophil chemoattractants KC (also known as Cxcl1) and Mip2 (also known as Cxcl2) following secondary challenge with S. pneumoniae. This resulted in inadequate neutrophil responses during the early phase of host defense against secondary bacterial infection. Indeed, influenza-infected wild-type mice cleared secondary pneumococcal pneumonia after pulmonary administration of exogenous KC and Mip2, whereas neutralization of Cxcr2, the common receptor for KC and Mip2, reversed the protective phenotype observed in Ifnar−/− mice. These data underscore the importance of the type I IFN inhibitory pathway on CXC chemokine production. Collectively, these findings highlight what we believe to be a novel mechanism by which the antiviral response to influenza sensitzes hosts to secondary bacterial pneumonia.

**Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice**

Arash Shahhangian,1,2 Edward K. Chow,3 Xiaoli Tian,4 Jason R. Kang,1 Amir Ghaifari,1,2 Su Y. Liu,1,2 John A. Belperio,4 Genhong Cheng,1,5 and Jane C. Deng4

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4Division of Pulmonary and Critical Care Medicine and 5Molecular Biology Institute, David Geffen School of Medicine, UCLA, Los Angeles, California, USA.

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**Lessons from the Flu:**

Changes in Immune Cell Function in Postinfluenza Bacterial Pneumonia

Flu usually not lethal, bacterial “super” infection often is (>50% of deaths)

Associated with high levels of interferons (types I and II), IL-10, TGF-beta

Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice

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**Important Mediator of the Enhanced Susceptibility to Secondary Pneumococcal Pneumonia after Influenza Infection**

J. Eijken,†‡ Leontine J. R. van Elden,† Monique Nijhuis,† Rob Schuurman,† Miranda Florquin,§ Michel Goldman,¶ Henk M. Jansen,† René Lutter,†‡ and Tom van der Poll,*†

S. pneumoniae is a serious complication during and shortly after influenza infection. We established a mouse model of secondary pneumococcal pneumonia and evaluated the role of IL-10 in host defense against Streptococcus pneumoniae after influenza infection. C57BL/6 mice were intranasally inoculated with 10 median tissue culture infectious doses of influenza A/PR/8/34 or PBS (control) on day 0. By day 14 mice had regained their normal body weight and cleared influenza virus from the lungs, as determined by real-time quantitative PCR. On day 14 after viral infection, mice were challenged with S. pneumoniae (serotype 3) intranasally. Mice recovered from influenza infection were highly susceptible to subsequent S. pneumoniae infection, as reflected by a 100% lethality on day 3 after bacterial infection, whereas control mice with established influenza infection had 3% and 83% lethality on day 6 after pneumococcal infection. Furthermore, 1000-fold higher bacterial inoculation rate with S. pneumoniae and, particularly, 50-fold higher pulmonary levels of IL-10 were observed in mice with established influenza infection in control mice. Treatment with an anti-IL-10 mAb 1 h before bacterial inoculation resulted in a significant reduction of secondary pneumococcal pneumonia and markedly reduced lethality during secondary bacterial pneumonia compared with those in IgG1 control mice. IL-10 is a potent modulator of host defense and renders normal immunocompetent mice highly susceptible to secondary pneumococcal pneumonia. This increased susceptibility to secondary bacterial pneumonia is at least in part caused by excessive IL-10 production and reduced neutrophil function in the lungs. The Journal of Immunology, 2004, 172: 7603–7609.
Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to severe *S. pneumoniae* pneumonia that phenocopies post-viral infection in non-DS individuals

Strong Inference

Interferonopathy

Toll-like receptors

Immune suppression IL-10/TGF-beta

Respiratory commensal bacteria

Trisomy 21 consistently activates the interferon response

Kelly D Sullivan¹,²,³,⁴*, Hannah C Lewis¹,², Amanda A Hill¹,², Ahwan Pandey¹,²,³,⁴, Leisa P Jackson¹,³,⁴, Joseph M Cabral¹,³,⁴, Keith P Smith¹, L Alexander Liggett¹,⁵, Eliana B Gomez¹,³,⁴, Matthew D Galbraith¹,²,³,⁴, James DeGregori¹,⁵,⁶,⁷,⁸,⁹, Joaquin M Espinosa¹,²,³,⁴*

*J. theor. Biol. 86, 603–606*
Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to severe *S.pneumoniae* pneumonia that phenocopies post-viral infection in non-DS individuals.

**Strong:**

- Interferonopathy
- Toll-like receptors
- Immune suppression IL-10/TNFα
- Respiratory commensal bacteria

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**Fig. 1.** Overview of the different PRRs involved in recognition of *S. pneumoniae*. Cell wall components and possibly PLY of extracellular bacteria are recognized by TLR2 and -4 respectively. Moreover, *S. pneumoniae* is internalized by phagocytic cells and subsequently degraded in phagosomes leading to the release of bacterial peptidoglycan and nucleic acids. While unmethylated CpG-containing DNA is sensed by TLR9 within the endosomes, other bacterial components might gain access to the cytosol possibly dependent on PLY-mediated membrane disruption. For example, pneumococcal peptidoglycan fragments are detected by NOD2 within the cytosol. Moreover, pneumococcal DNA is detected by AIM2 and by an additional still not identified cytosolic PRR. TLRs as well as NOD2 subsequently stimulate the production of NF-κB-dependent cytokines including TNFα, IL-6, KC and pro-IL-1β. While functional TNFα, IL-6 and KC are released after translation, the production of IL-1β requires a second signal. This is provided by the NLRP3 and the AIM2 inflammasomes activated by PLY and bacterial DNA, respectively, which mediate cleavage of pro-IL-1β into mature IL-1β. Sensing of *S. pneumoniae* DNA by the yet-to-be-identified cytosolic DNA sensor activates the adaptor STING and the transcription factor IFR3, and stimulates type I IFN responses.
In persons with DS, the lung is in a chronic state of susceptibility to infections, due to altered humoral and cellular immunity. The aim of the study was to determine the cytokine production in whole blood of children with DS upon stimulation with heat-killed Streptococcus pneumoniae and lipopolysaccharide (LPS), in comparison with their healthy siblings.

METHODS: Whole blood of 61 children with DS and 57 of their healthy siblings was stimulated with 200 µg/ml LPS and 4 × 10⁷ colony-forming units/ml S. pneumoniae during 6, 24, and 48 h. Concentrations of pro- and anti-inflammatory cytokines, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-12p70, and IL-10 were determined at all time points.

RESULTS: Children with DS show an increased IL-10 production upon stimulation with S. pneumoniae compared to their healthy siblings. At most time points, no significant differences were seen in cytokine production upon stimulation with LPS.

CONCLUSION: Children with DS may be prone to a severe course of pneumococcal pneumonia, because of an increased anti-inflammatory response.
Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to severe S. pneumoniae pneumonia that phenocopies post-infection susceptibility to severe respiratory infections in non-immune-competent infants. This is associated with impaired respiratory innate immune response triggered by viral infection in non-immune-competent infants.

Respiratory Commensal Bacteria
Corynebacterium pseudodiphtheriticum Improves Resistance of Infant Mice to Respiratory Syncytial Virus and Streptococcus pneumoniae Superinfection

Paulraj Kanmani1,2†, Patricia Clua3,4†, Maria G. Vizoso-Pinto5, Cecilia Rodriguez1,2, Susana Alvarez3,4, Vyacheslav Melnikov7,8, Hideki Takahashi9,10, Haruki Kitazawa1,2* and Julio Villena1,3,4*

*Correspondence: Haruki Kitazawa

1Tohoku University, Sendai, Japan, 2Faculty of Medicine, INSIBIO (UNT-CONICET), National University of Tucuman, Argentina, 3Laboratory of Plant Pathology, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan, 4Plant Immunology Unit, International Education and Research Center for Food and Agricultural Immunology, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan, 5Laboratory of Immunobiotechnology, Reference Centre for Laboratory Animals, Minsk, Belarus, 6Laboratory of Plant Pathology, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan, 7Department of Clinical Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, 8Laboratory of Applied Chemistry, Graduate School of Agriculture, Tohoku University, Sendai, Japan, 9Laboratory of Animal Products Safety, Laboratory of Food Microbiology, CRIET, FAUB, La Plata, Argentina, 10Livestock Immunology Unit, International Education and Research Center for Food and Agricultural Immunology, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan, 11Gabrichevsky Institute of Epidemiology and Microbiology, Moscow, Russia

†These authors contributed equally to this work.
<table>
<thead>
<tr>
<th>Post-influenza, non-DS</th>
<th>DS</th>
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<tbody>
<tr>
<td>Fulminant Remodeling</td>
<td>?</td>
</tr>
<tr>
<td>Platelet Activating Factor Receptor (PAFR)</td>
<td>?</td>
</tr>
<tr>
<td>IFN signaling increase</td>
<td>?</td>
</tr>
<tr>
<td>IL-10 signaling increase</td>
<td>?</td>
</tr>
<tr>
<td>TLR down</td>
<td>?</td>
</tr>
<tr>
<td>Immune cell dysfunction</td>
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</table>
Respiratory syncytial virus (RSV) bronchiolitis

Symmetrical hyperinflation of the lungs, streaky perihilar opacities and

difference in the histological appearance of the lungs compared to unaffected people. In people with Down syndrome, this association in children with Down syndrome is unclear.

Post-infectious complications, pulmonary arterial hypertension is to identify and manage the cardiac shunt (especially A VSD) exacerbates the risk of pulmonary hypertension. Pulmonary arterial hypertension can be managed with diuretics and pulmonary vasodilators.

Pulmonary hypoplasia

Organ

Subpleural cysts

Congenital heart defects

Upper airway obstruction occurs in 14% of children with Down syndrome. Some of the more common upper airway abnormalities in Down syndrome contribute to the severity of this association in children with Down syndrome.

Prenatal sonogram and upper esophageal pouch. An enteric duodenum. On fluoroscopy there is circumferential encircling the esophagus and trachea.

Midgut anomalies

Malrotation, with an estimated incidence 45 times greater than the general population. The obstruction. Upper gastrointestinal study is typically the next study performed and shows an abnormal location of the upper esophageal pouch. An enteric

Congenital gastrointestinal anomalies are present in 4% of newborns. Table 3. Congenital gastrointestinal anomalies are present in 4% of newborns. Table 3. Congenital gastrointestinal anomalies are present in 4% of newborns.

The most common gastrointestinal anomaly in Down syndrome is malrotation, with an estimated incidence 45 times greater than the general population.

Although this is often an incidental finding, careful evaluation of the abdomen is important in these patients. Children with malrotation and midgut volvulus usually present with difficulty feeding and increased frequency of vomiting.

We need to explore mouse models of DS more fully for these applications.
Post-Influenza-Like Lung in Down Syndrome?

Organ

Tissue

Cells

Saline

S. pneumoniae polysacc

Lung Remodeling Score

Control Dp(10) Dp(16) Control Dp(10) Dp(16)

Saline S. pneumoniae polysacc

Green = CD15 Blue = DAPI (nuclei)

Hematoxylin & Eosin
Increased PAFR facilitates increased S. pneumoniae adhesion

Involvement of the platelet-activating factor receptor in host defense against Streptococcus pneumoniae during postinfluenza pneumonia

Koenraad F. van der Sluijs,1,2,3 Leontine J. R. van Elden,4 Monique Nijhuis,4 Rob Schuurman,5 Sandrine Florquin,5 Takao Shimizu,6 Satoshi Ishii,7 Henk M. Jansen,9 René Lutter,9 and Tom van der Poll1

1Laboratory of Experimental Internal Medicine; 2Department of Pulmonology; 3Laboratory of Experimental Immunology; 4Department of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam; 5Eijkman-Winkler Institute, Department of Virology, University Medical Center, Utrecht, The Netherlands; 6Department of Biochemistry and Molecular Biology, Faculty of Medicine, The University of Tokyo; and 7CREST of Japan Science and Technology Corporation, Tokyo, Japan
Post-Influenza-Like Lung in Down Syndrome?

### Cells
- Lung stains
- Peripheral blood
- Human
- Fibrocytes
- Fibroblasts
- Lung Cells
- Dp16
- PB/BALF

### Migration
- Relative Migration in Response to MCP-1, 18 hours
- n = 10
- Ctl: 100 ± 10
- DS: 50 ± 10
- *p < 0.05

### Phagocytosis
- n = 10
- Ctl: 100 ± 10
- DS: 50 ± 10
- *p < 0.05

### CD11b+/CD14+/CD206+
- n = 11
- Ctl: 8 ± 2
- DS: 4 ± 2

### Pro-collagen+
- n = 42
- Ctl: 6 ± 1
- DS: 3 ± 1

### CD11b+/CD15+/CD163+
- n = 27
- Ctl: 20 ± 5
- DS: 15 ± 5

### WBC
- AAM*
- n = 11
- Ctl: 2 ± 0.5
- DS: 1 ± 0.5

- Fibrocytes*
- n = 23
- Ctl: 6 ± 1
- DS: 3 ± 1

- LDG*
- n = 27
- Ctl: 15 ± 3
- DS: 10 ± 3
Cell/Individual particle tracking Icy
Post-Influenza-Like Lung in Down Syndrome?

Organ

Tissue
Lung stains

Human
Peripheral blood
Fibroblasts

Cells

Dp16
PB/BALF
Lung Cells

Low density granulocyte migration, relative to control

Migration

Relative Migration Distance
In response to MCP-1, 18 hours

Phagocytosis

% CD14+
Phagocytosing

Non-Trisomic
Dp16

55% decrease
Post-Influenza-Like Lung in Down Syndrome?

Post-influenza, non-DS

- Fulminant Remodeling
- PAFR
- IFN signaling increase
- IL-10 signaling increase
- TLR down
- Immune cell dysfunction

DS
Is there A Link Between Lung Disease and Cognition in Down Syndrome?

Table 1. Patient characteristics and additional morbidity of 8 year old Down syndrome population in relation to parent-reported presence of recurrent respiratory tract infections (RRTI).

<table>
<thead>
<tr>
<th>RRTI+</th>
<th>RRTI−</th>
<th>Total</th>
<th>Chi-squared test</th>
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<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>P-value</td>
</tr>
</tbody>
</table>

Male: 85 (57) 84 (48) 169 (51) NS
Female: 64 (43) 92 (52) 156 (49)
Age at inclusion*: (mean, range and SD in years) 8.14 (7.8–8.8) ± 0.14 8.15 (7.8–9.1) ± 0.15 8.14 (7.8–9.1) ± 0.15
School attendance

<table>
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<th>Cause of Additional Morbidity</th>
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<tr>
<td>RRTI+</td>
</tr>
<tr>
<td>------</td>
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<tr>
<td>n (%)</td>
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Significant impact of recurrent respiratory tract infections in children with Down syndrome

R. H. J. Verstegen,* H. B. M. van Gameren-Oosterom,† M. Fekkes,‡ E. Dusseldorp,¶ E. de Vries* and J. P. van Wouwe†

*Department of Pediatrics, Jeroen Bosch Hospital, †Department of child Health, Netherlands Organisation for Applied Scientific Research TNO, ‡Department of Pneumology, University Hospital Maastricht, §Department of Paediatrics, Jeroen Bosch Hospital, ¶Department of Child Health, University of Amsterdam, NS, not significant.

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*There was no significant difference in age between both groups determined by a t-test.
†Percentage out of all children attending regular education.
‡Parental reported morbidity.
RRTI+, children with respiratory tract infections; RRTI−, children without respiratory tract infections; NS, not significant.
Is there A Link Between Lung Disease and Cognition in Down Syndrome?

Table 2. Results of multiple regression analyses for scale scores of the McCarthy Scales of Children’s Abilities (MSCA) of 8-year-old Down syndrome children with and without parent-reported recurrent respiratory tract infections (RRTI)

<table>
<thead>
<tr>
<th></th>
<th>RRTI*</th>
<th>RRTI+</th>
<th>Regression coefficient† (β)</th>
<th>Effect size‡ (f²)</th>
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<tbody>
<tr>
<td></td>
<td>Total (n = 130)</td>
<td>Male (n = 75)</td>
<td>Female (n = 55)</td>
<td>Total (n = 140)</td>
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<tr>
<td>Verbal</td>
<td>33.06 (19.13)§</td>
<td>29.64 (19.96)</td>
<td>37.47 (17.18)</td>
<td>40.68 (16.18)</td>
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<tr>
<td>Perceptual</td>
<td>26.76 (16.58)</td>
<td>21.80 (15.84)</td>
<td>33.33 (15.43)</td>
<td>32.34 (14.90)</td>
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<tr>
<td>performance</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Quantitative</td>
<td>9.44 (6.80)</td>
<td>7.86 (6.46)</td>
<td>11.44 (6.75)</td>
<td>12.22 (6.57)</td>
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<tr>
<td>Memory</td>
<td>10.74 (7.77)</td>
<td>9.27 (7.69)</td>
<td>12.64 (7.53)</td>
<td>13.94 (7.37)</td>
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<tr>
<td>Motor</td>
<td>23.23 (12.57)</td>
<td>20.03 (12.64)</td>
<td>27.47 (11.32)</td>
<td>27.67 (11.78)</td>
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<tr>
<td>General cognitive</td>
<td>69.30 (40.25)</td>
<td>59.36 (40.22)</td>
<td>82.29 (36.84)</td>
<td>85.24 (43.43)</td>
</tr>
<tr>
<td>score</td>
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Developmental age (SD in months)

- 3 years 8 months (10.91)
- 3 years 6 months (10.53)
- 4 years (10.53)
- 3 years 11 months (10.66)

Lower scores indicate more impaired development.
*P < 0.05; **P < 0.01; ***P < 0.001.
†β = unstandardized regression coefficient of the effect of RRTI, correcting for (at least) age (at least) monthly), siblings, gender, congenital heart defect, diagnosis of asthma, gastrointestinal problems, key messages
‡Effect size (f²): small effect (0.01–0.10), moderate effect (0.10–0.33) and large effect (0.33–1.0).
§Mean scores are presented with standard deviation between brackets.

Key messages

- Children with Down syndrome are known to be at increased risk of recurrent respiratory tract infections.
- In 8-year-old children with Down syndrome, parental report of recurrent respiratory infections was associated with more delayed development, increased risk of behavioural problems and lower health-related quality of life.
Lung Disease & Cognition: Tantalizing Clues

Cognitive Assays in Dp16 mice

**Distance Moved**

- Ctl: 4000 cm
- Ts: 6000 cm

**Velocity**

- Ctl: 5 cm/s
- Ts: 10 cm/s

- * indicates a significant difference

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Do lower learning and memory scores correlate to inflammatory cytokines?

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Do repeat lung infections worsen cognitive score?

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**TNFalpha**

- Ctl Lung: 20 pg/mg tissue
- Ts Lung: 60 pg/mg tissue

**IL-1b**

- Ctl Lung: 20 pg/mg tissue
- Ts Lung: 60 pg/mg tissue

- * indicates a significant difference
Take Home Messages

Individuals with DS are significantly challenged by infectious lung disease
   Post-influenza state of susceptibility to severe bacterial lung infection
   Chronic respiratory infection linked to myositis/myopathy, myocarditis, CNS inflammation

Infectious lung disease likely impacts cognition
   Reducing burden in DS would greatly improve QOL
   Reducing burden in DS may preserve cognition

The future is BRIGHT!! Great things have happened, and MUCH more is on the way
   ex: Amniotic fluid stem cells “trained” to patch congenital heart defects-submit July 23rd
   ex: Autoimmunity and Lung Disease
Many Thanks
Kelley Colvin

Persons with DS and their families

Support

Global

Sie Center

Crnic Institute

Funding